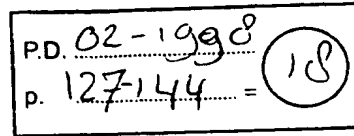


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# **The new asthma genetics and its implications for public health**

Michael J Abramson, PhD  
Stephen B. Harrap, PhD

## **ABSTRACT**

*Objective:* To review the genetics of asthma from a public health perspective.

*Data Sources:* Studies of asthma genetics published between 1990 and 1997 were reviewed.

*Study Selection:* Studies based on random population sampling were preferred. Both linkage and association studies were included, as were genome scans. Studies needed to report results for asthma or the related traits of atopy and bronchial hyperreactivity (BHR).

*Data Extraction:* The chromosomal locations linked to or candidate genes associated with asthmatic traits were tabulated.

*Data Synthesis:* A clear majority of studies relied on clinical ascertainment or highly inbred populations. Although there is no consensus about the definition of asthma, phenotypic characterisation of subjects is more complete in recent studies. The high affinity IgE receptor gene on chromosome 11q and a cluster of cytokine genes on chromosome 5q are linked both to atopy and BHR. The T cell receptor gene on chromosome 14q is linked to specific IgE responses, and a region on chromosome 12q is linked both to total IgE levels and asthma. Genome scans have identified other regions of interest on chromosomes 2q, 4, 5p, 6, 7, 11p, 13, 16, 17, 19q, and 21q.

Dr. Abramson is Associate Professor, Department of Epidemiology and Preventive Medicine, Monash Medical School, Alfred Hospital, Prahran 3181, Melbourne, Australia.

Dr. Harrap is Professor and Head, Department of Physiology, University of Melbourne, Melbourne, Australia.

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**Conclusions:** Asthma is a complex polygenic disorder with marked gene-environment interactions. However it is proving tractable to powerful new genetic approaches arising from the human genome project. At the present state of knowledge, population screening for the asthma genes so far identified cannot be justified. Gene therapy for asthma is an even more remote prospect.

**Keywords:** asthma, genetics, atopy, bronchial hyperreactivity, public health

## INTRODUCTION

Asthma is a major public health problem in Australia and many other Western countries. Epidemiological studies have found that 22-24% of Melbourne schoolchildren have wheezed in the preceding 12 months (1) and 13% of Victorian adults report having asthma at some time (2). It is the commonest reason for hospital admission among children aged between 1 and 14 years. The cost of asthma to Australia has been estimated by the National Asthma Campaign to be between A\$585 and A\$720 million per year (3). Furthermore, asthma contributed to the deaths of 749 Australians in 1995, one of the highest asthma mortality rates in the world.

Asthma is a complex respiratory condition, in which the airways narrow excessively in response to a wide range of environmental stimuli. Asthma is closely associated with allergies and other allergic conditions such as hayfever and eczema. For over 300 years, asthma and allergies have been known to run in families (4). Epidemiological studies have consistently found that a parental history of asthma increases the risk about 2-fold in young adults (5). If both parents have asthma, then the children are 7 times more likely to develop asthma (6). Recent advances in human genetics have now made it possible to identify some of the genes responsible. The cell biology, statistical aspects, and clinical implications of asthma genetics have been well discussed elsewhere (4,7,8). In this review, we wish to particularly consider the implications for public health.

## THE NEW GENETICS AND PUBLIC HEALTH

As the end of a century of astonishing progress in medical science approaches, genetics promises to become the foundation of new

strategies for improving public health. At the beginning of this century, genetics was largely concerned with peas and fruit flies. Shortly thereafter, inborn errors of human metabolism were described, many of which subsequently proved to be due to single gene defects. With the advent of the human genome project, it has finally become possible to understand the genetics of common diseases, which are mostly characterised by polygenic (multiple gene) inheritance and substantial gene-environment interactions.

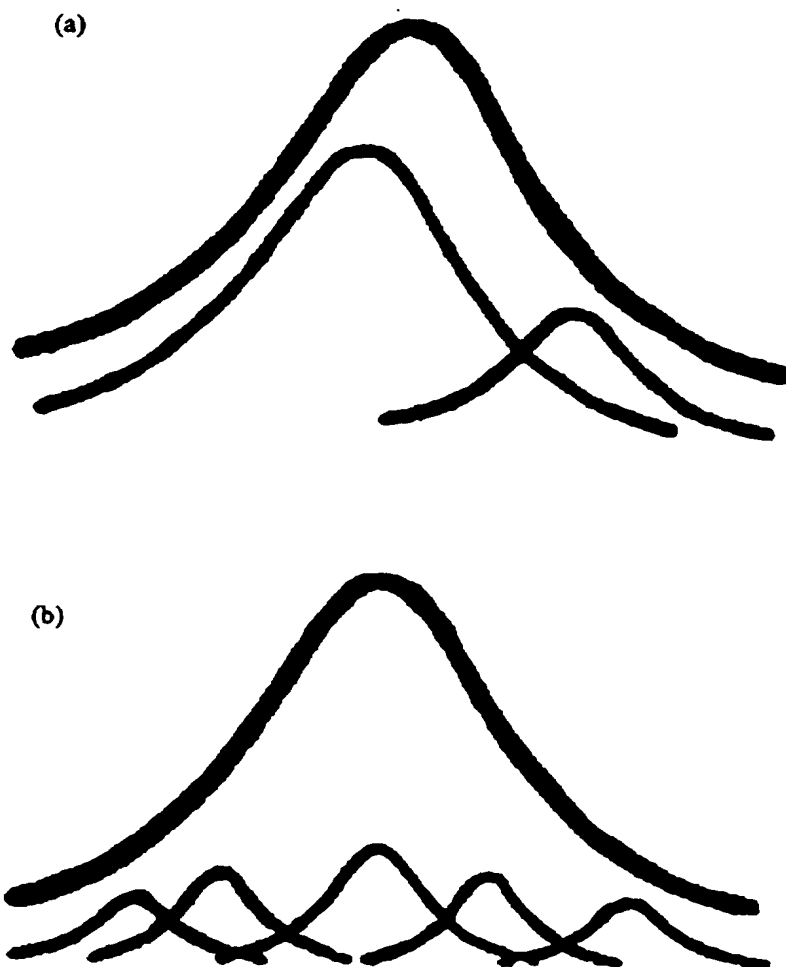
The new genetics is well suited to challenges presented by conditions such as asthma. However, success is dependent on new collaborative endeavours. The biological cascade from DNA, through RNA, cells, tissues, organs, disease, and public health is obvious. However, research collaboration does not mirror this vertical progression, tending to be stratified with molecular biologists, physiologists, clinicians, and epidemiologists isolated on each level. A prerequisite to successful genetic research in asthma is vertical collaboration. Clinicians and epidemiologists should assist molecular biologists and physiologists in the development of hypotheses and interpretation and implementation of results.

## POPULATION GENETICS

The population distribution of a genetically determined continuous trait depends upon the mode of inheritance (Fig. 1). If there is a single major gene, there is an identifiable subpopulation of affected individuals. For example, it has been reported that the distribution of total serum immunoglobulin E (IgE) in some populations is consistent with a major autosomal recessive gene being associated with elevated levels (9). On the other hand, multiple minor genes (polygenes) are often seen in common traits, and the distribution of total IgE in Mormons is more consistent with polygenic inheritance (10).

## POLYGENIC INHERITANCE

The quantitative nature of the underlying phenotypes of asthma is likely to reflect the combined effects of a number of polygenes. It is supposed that each polygene contributes incrementally to the phenotype. However, the number and nature of polygenes is an



**Fig. 1.** The population distribution of a continuous trait (such as total serum IgE) which would be expected if inheritance is due to (a) a single major gene resulting in an identifiable subpopulation or (b) multiple minor genes, each making a relatively small contribution to the trait.

unresolved question. Yet the answer impinges upon the usefulness of genetic information. For example, if bronchial hyperreactivity (BHR) were determined by 3 polygenes, each contributing a third to the genetic variation in BHR, then identifying one gene would be a significant discovery. However, there would be little likely benefit in defining one of 20 polygenes, each of which contributed only 5% to variation in BHR.

There are other important implications of polygenetic inheritance in relation to genetic risk. Although the inheritance of a particular gene represents a qualitative characteristic, the implication for risk is not dichotomous. Polygenes contribute to the quantity of risk. In the instance of future screening, genetic markers will indicate predisposition and not predestination. The effect of individual genes will depend on the interaction with other genes and environmental circumstances.

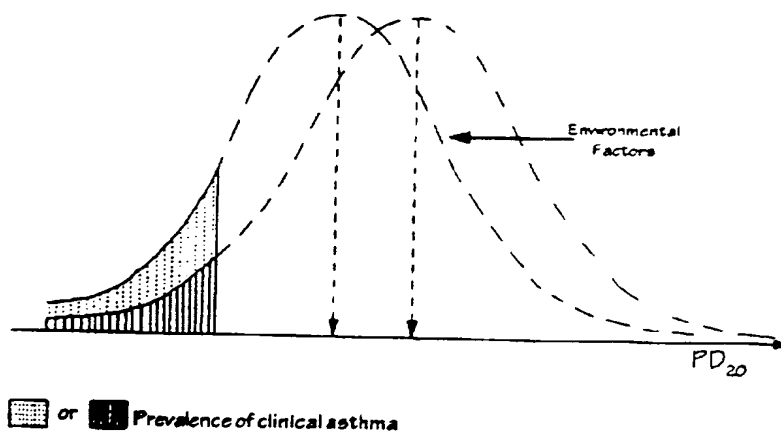
## ENVIRONMENTAL FACTORS

The environment includes the social, cultural, psychological, biological, and behavioural components of lifestyle and external circumstances. The known environmental risk factors for asthma include small families; access to health care services; exposure to house dust mites, cats, and pollen; and lifestyle factors such as cigarette smoking. The effects of environment are most obvious in the migration studies or changes in genetically and geographically stable populations over time. Variation in environmental exposure is often greater between than within populations.

A good example is the Pacific Island of Tokelau, which was devastated by a cyclone in 1966, after which most of the population were evacuated to New Zealand. Tokelauan children born in Auckland have a significantly higher risk of asthma than children born in Tokelau (11). In contrast, genetic variation is often greater within populations than between. For these reasons, the population average of a quantitative phenotype reflects environmental influence while individual variation indicates genetic differences.

The problem for the new genetic research is that genetic predisposition may not be expressed unless the population is exposed to a conducive environment. Almost all individuals with a defective gene for the Cystic Fibrosis Transmembrane Regulator protein are predestined to develop cystic fibrosis. However individuals whose genetic makeup places them at the upper end of the population distribution may cross the threshold of clinical asthma only in an environment that accords a high population average of bronchial reactivity, i.e., a lower mean dose of histamine or methacholine provoking a 20% decline in lung function ( $PD_{20}$ ). Under different circumstances, a lower population average for bronchial reactivity may leave those with the same genetic predisposition short of the asthmatic threshold, i.e., showing a higher mean  $PD_{20}$  (Fig. 2). This is a typical example of gene-environment interaction, which until recently has been difficult to disentangle.

Another consideration is that genetic markers defined in one population may not be relevant to a separate population because of environmental differences. We cannot simply extrapolate results from elsewhere.



**Fig. 2.** Environmental factors may result in only a small increase in the average bronchial reactivity (lower mean  $PD_{20}$ ) in the population, but this can substantially increase the hyperreactive tail with clinical features of asthma.

## **NEW GENETIC METHODS**

The challenges to unravelling the genetic complexities of asthma are great. The difficulties include the interaction between underlying phenotypes such as BHR, atopy, and total IgE, each of which may be determined by separate genes. In addition, the expression of genetic predisposition is linked intimately to exposure to environmental triggers. Nevertheless, genetic discovery has been facilitated by advances in DNA technology and statistical methods of linkage analysis that have realised genome-wide searches for chromosomal loci controlling quantitative traits.

The human genome comprises about 70,000 genes made up of 3 million base pairs over 23 pairs of chromosomes. Until recently, searching for disease genes was like searching for a needle in a haystack. An important spinoff of the human genome project has been the development of gene maps. It is important to remember that the map is not the territory. The map references or markers are usually relatively short repetitive sequences of apparently non-functional DNA scattered across all 23 chromosomes. A skeletal set of 400 markers whose chromosomal locations are known is now commercially available and is being used to conduct genome scans.

The genomic maps and new statistical methods provide powerful tools for tracking the inheritance of a trait in family linkage studies. However the result is often only the identification of a chromosomal region of interest. The resolution of such analyses is limited, and within particular regions there are often many hundreds of genes, only a few of which may have known functions. At this stage, investigators are often faced with a difficult challenge to identify the responsible gene and discover the causative mutation(s). Sometimes known genes in the locality provide candidates for more intensive study. However it is also possible that other, previously undetected, genes may explain the genetic linkage. Their identification may be a crucial step in discovering new mechanisms of disease and therefore new possibilities for prevention and treatment.

Once a mutation in a candidate gene is found, it should be tested in case-control (association) studies. It is also necessary to examine the physiological consequences of mutations. Functionally silent mutations found more commonly in cases than controls may only be

markers of an aetiological mutation elsewhere in the same chromosomal vicinity.

Often an apparently simple trait may be the result of a genetically heterogeneous group of mutations. Each might only be detected by one DNA test, making screening a potentially costly and complicated business. However, the functional consequences of these mutations for gene expression or their peptide products may be similar. Therefore the collaboration between the molecular biologists and physiologists not only indicates the relevance of certain mutations but also forms the foundation for preventive or therapeutic intervention.

What sampling and statistical methods should be used to detect the genetic influences on human diseases in the population? Traditionally, clinical geneticists have focused on multigenerational pedigrees with multiple affected family members. This approach has been very successful in identifying the mode of inheritance of rare single gene disorders. Recent statistical developments have been driven by the need for flexibility in both sampling and genetic modeling.

The new relative pair methods avoid the need for multigenerational pedigrees. Instead, quantitative data from small subsets of families can be used. In contrast to multigenerational analyses, the exact mode of inheritance need not be defined a priori. However, a particular advantage for public health research is that the new methods allow more representative sampling of a general community. Large pedigrees with high disease rates have often led to the discovery of genes of little relevance to the population at large.

### ASTHMA GENES

Studying the genetics of asthma has been frustrated by a lack of consensus over the definition. However there is general agreement that asthma usually contains at least two underlying traits: atopy and bronchial hyperreactivity (BHR). Atopy is the ability to mount an IgE response against allergens such as house dust mite, cat, or pollen, which can be demonstrated by positive skin prick tests to extracts of these allergens. BHR is the exaggerated sensitivity of the airways to nonspecific stimuli such as methacholine, exercise, or cold air, which can be demonstrated by a positive bronchial challenge test. Another feature of asthma is chronic airway inflammation with eosinophils. It is quite likely that these various asthmatic traits are under separate



genetic control. This is supported by the recent observation that both extrinsic (atopic) and intrinsic (nonatopic) asthma can be inherited (12).

It is thus necessary to measure underlying phenotypes in all subjects in an attempt to dissect the independent genetic determination of each characteristic and their possible interaction. Most studies in the literature have been severely affected by ascertainment bias. Recruitment of asthmatics through a respiratory clinic may select a different set of genes than recruitment of asthmatics through an allergy clinic. Clearly, the most sensible approach is recruitment from the general population with thorough phenotypic characterisation. This not only provides an indication of the relative contribution and potential interaction of each underlying phenotype, but also identifies genetic markers in the relevant "consumers" of public health preventive strategies.

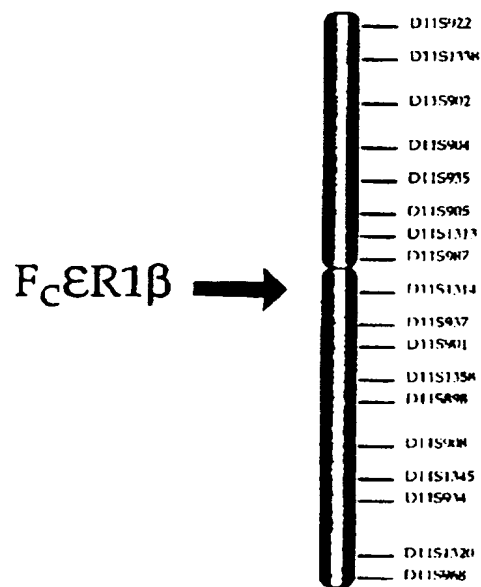
The results of a number of recent genetic studies of traits underlying asthma are summarised in Table 1. A partial map of chromosome 11 showing a region of interest is presented in Fig. 3. Investigators from Oxford University originally reported that atopy was linked to a marker on chromosome 11q (13). Subjects were recruited through a proband attending an allergy clinic or media appeals, thus introducing substantial volunteer bias. One curious finding was that inheritance

**Table 1**  
*Studies of asthmatic traits reporting chromosomal location and possible candidate genes.*

Trait	Chromosomal location	Candidate genes
Atopy	11q13	Fcε-R1β subunit
BHR	11q13	?Fcε-R1β subunit
Total IgE levels	5q31-33	Interleukins 3, 4, 5, 9, 13,
BHR	5q31-33	IRF1, CDC25, gmCSF, EGR1, PDGFR, FGFA
Specific IgE responses	14q	TCR α/δ complex
Asthma, Total IgE	12q	IFNγ, MCGF, NFYβ

Abbreviation: BHR = Bronchial hyperreactivity, IgE = Immunoglobulin E, IRF1 = Immune regulatory factor 1, CDC25 = Cell division cycle 25, gmCSF = Granulocyte-macrophage colony stimulating factor, EGR1 = Early growth response gene 1, β<sub>2</sub>ADR = β<sub>2</sub> Adrenoreceptor, GRL1 = Lymphocyte specific glucocorticoid receptor, PDGFR = Platelet derived growth factor receptor, TCR = T cell receptor, IFNγ = Interferon γ, MCGF = Mast cell growth factor, NFY = Nuclear Factor Y.

*Public Health Reviews 1998: 26*



**Fig. 3.** A region of chromosome 11 showing the high-affinity IgE receptor gene ( $Fc\epsilon R1\beta$ ) and a number of anonymous markers possibly linked to asthmatic traits.

appeared to be confined to maternally derived alleles. The Oxford group subsequently described mutations in the high affinity IgE receptor ( $Fc\epsilon R1$ )  $\beta$  subunit gene associated with atopy (14). This gene is a plausible candidate since the receptor for which it codes is present on the surface of mast cells in high concentrations. The binding of IgE molecules triggers the release of histamine and other inflammatory mediators from mast cells, which in turn trigger attacks of asthma.

However many other investigators have been unable to confirm significant linkage between chromosome 11q and atopy (15–17). These negative results were not influenced by the definition of atopy as a positive skin prick test, elevated total IgE level, or positive RAST. There are several possible explanations for this discrepancy (18). Incorrect specification of the genetic model can falsely inflate the

apparent strength of linkage. Simple autosomal dominance is unlikely to apply to atopy. Genes which map different regions of the genome may each be sufficient for the expression of atopy. Several major and minor genes may need to interact for atopy to be expressed. Finally, as discussed above, the development of allergy is dependent on multiple environmental factors, which may vary between populations.

Chromosome 5q contains a number of genes coding for cytokines (soluble messengers) involved in the inflammatory response seen in asthma and also the  $\beta_2$  adrenergic receptor found on bronchial smooth muscle. Studies in the highly inbred Amish population (19) suggested linkage of total IgE levels to the gene for the cytokine Interleukin 4. A study by Postma et al (20) found linkage of BHR to another nearby marker (D5S436). The Dutch subjects comprised 84 families for whom a proband with symptomatic asthma and BHR to histamine had been previously identified by a regional referral clinic.

The T lymphocyte can be appropriately considered as the conductor of the immunological orchestra in asthma. A British-Australian study described linkage of specific IgE responses to the T cell receptor  $\alpha/\delta$  gene in both clinical and general population samples (21). A strength of this study was that the Australian subjects were drawn from the general population of Busselton. A number of markers on chromosome 12q have been linked to both asthma and total serum IgE in an Afro-Caribbean population, and linkage to IgE has been confirmed in the Amish (22). The Caribbean families were recruited from 29 asthmatic probands identified by clinics in Barbados.

There are undoubtedly many other asthma genes still waiting to be discovered. Two scans of the entire human genome for genes linked to asthmatic traits have now been reported. Daniels et al (23) studied linkage to bronchial reactivity (slope of the methacholine dose response curve), total serum IgE, atopy (including skin prick tests, allergen specific IgE and total IgE), and blood eosinophil counts. They found regions of chromosomes 4, 6, 7, 13, and 16 (Table 2) which warrant more detailed mapping for candidate genes. The Collaborative Study on the Genetics of Asthma (24) recently reported linkage of asthma to chromosomes 5p15 and 17p11.1-q11.2 in African-Americans, chromosomes 11p15 and 19q13 in Caucasians, and chromosomes 2q33 and 21q21 in Hispanics (Table 2). Strengths of this study were the inclusion of diverse ethnic groups and a clinical definition of asthma based upon symptoms, BHR, or reversible

bronchoconstriction and exclusion of competing pulmonary diagnoses.

**Table 2**

*Simplified results of genome scans (23,24) for other chromosomal regions linked to asthmatic traits*

Chromosome	BHR	Total IgE	Atopy	Eosinophils	Asthma
2q					+
4	+				
5p					+
6		+			
7	+	+	+	+	
11p					+
13			+		
16	+	+			
17					+
19q					+
21q					+

#### ASTHMA GENETICS IN MELBOURNE, AUSTRALIA

Our research group provided the first independent confirmation of linkage of asthmatic traits to chromosome 11q in a true general population sample (25). We selected 4,500 young adults at random from the electoral rolls for Melbourne, of whom 3,200 subjects returned a respiratory screening questionnaire. A total of 757 individuals were fully phenotyped for atopy with skin prick tests and BHR by methacholine challenge tests. We then approached their siblings resident in Melbourne and recruited a total of 123 affected sibling pairs who shared at least one phenotype. Genotyping at the Fcε-RIβ locus was performed using the polymerase chain reaction (26), and alleles were visualised by laser scanning.

Our results (25) are summarised in Table 3. We found a significant excess of shared alleles in sib pairs affected by asthma, BHR, and atopy. However on closer examination, the linkage was substantially due to those sib pairs who had BHR without atopy, rather than those who had atopy without BHR. Furthermore, we have been unable to detect the mutations in the Fcε-RIβ gene described by the Oxford

group. We have found polymorphisms in the gene, but these are unlikely to be of any functional significance (27). Thus we believe that there is likely to be another gene on chromosome 11q linked to BHR. Despite a number of potential candidate genes in this chromosomal region, we have not yet been able to map the precise location (28).

**Table 3**

*Fcε-RIβ allele sharing in affected sib pairs from Melbourne (25)*

Phenotype	Observed	Expected	% Excess	P
Asthma	98	83	18	0.002
BHR	80	66	22	0.001
BHR without atopy	28	21	33	0.004
Atopy	145	131	10	0.02
Atopy without BHR	93	87	7	0.12
Atopy and BHR	52	45	17	0.03

## IMPLICATIONS FOR PUBLIC HEALTH

These genetic studies of asthmatic traits are providing important insights into the molecular mechanisms of asthma. Benefits for public health could potentially arise from the introduction of genetic testing or the development of gene therapy. Genetic testing should be evaluated against similar criteria that apply to any screening program. The disease in question should not be too common or too rare. To be feasible in this era of shrinking health care budgets, the testing must not be too costly. Because of the implications of false negative and false positive results, the tests must be reliable. Finally, the results should be kept confidential. There have already been cases where insurance companies have sought to deny liability on the grounds that defective genes constitute a pre-existing condition.

The ethical implications of genetic testing for pulmonary diseases have been discussed more fully by Kimyai-Asadi and Terry (29). They believe that patients must be informed of the nature of the available genetic tests, the associated medical and psychosocial benefits and risks, as well as any available alternatives. Specialist physicians are less likely to provide patients with nondirective counselling than are

trained genetic counsellors. There are currently few controls on the marketing of genetic tests for common human disorders, which could be used inappropriately without any medical supervision. They suggest that workplace-based genetic testing should only be offered with the goal of improving occupational safety and should not be used to discriminate against workers with genetic disabilities.

However there are some more fundamental problems which will delay the introduction of population-based genetic testing for asthma. The genes and mutations identified to date only explain inheritance of asthmatic traits to a very limited extent. Furthermore we do not yet have environmental interventions which have been shown to modify the natural history of the disease. Early environmental modifications in high-risk infants identified by family history have, to date, been ineffective in preventing asthma. These interventions include maternal dietary restriction, promotion of breast feeding or use of hydrolysed infant feeding formulae (30), house dust mite sprays (31), and avoidance of environmental tobacco smoke. Thus, population screening for asthma cannot yet be justified.

Might it soon become possible to offer gene therapy for asthma? Because of the complex polygenic inheritance of asthma, multiple genes would need to be replaced, repaired, or repressed. Intervention would need to occur before immunological maturation, with all the attendant difficulties of treating young infants. There is a further technical problem of finding appropriate genetic vectors for all the multiple targets, including mast cells, T cells, and bronchial smooth muscle. It is rather sobering to consider that despite substantial research investment, we do not yet have an effective form of gene therapy for simpler monogenic disorders such as Cystic Fibrosis.

There is an important distinction between gene therapy directed at somatic cells, such as those lining the respiratory tract and germ-line gene therapy directed at sperm, ova, or early embryos. Kimyai-Asadi and Terry (29) consider that somatic gene therapy is ethically acceptable and could be offered to respiratory patients when effective methods become available. However they caution that germ-line gene therapy should be withheld until there is sufficient confidence that there are no serious genetic risks to future generations. These concerns have been given particular relevance by the successful cloning of a sheep from an adult animal and the ensuing debate over the ethics of human cloning.

The dividend of the investment in molecular biology may not be repaid in the currency of high technology. Issues of confidentiality, reliability, and cost will determine the feasibility of widespread genetic screening. Genetic testing might not be used for predictive testing, but may help target interventions. Certain genetic markers in asthma may be associated with greater (or lesser) efficacy of reliever or preventive medications. Molecular tests might also predict subjects predisposed to particular treatment side-effects. Indeed, a mutation in the  $\beta$  adrenergic receptor gene has been associated with the development of diminishing responsiveness to long-acting  $\beta$  agonist bronchodilator therapy (32).

Once causative mutations are found, it should be possible to chart their effects on proteins, cells, organs, and integrated body function. At each step, the interaction with environmental factors can be assessed. The potential for genomic mapping to reveal hitherto unknown genes offers the possibility to identify novel behavioural or lifestyle means of modifying genetic predisposition. The benefit of the new genetics may be in the development of new, simple, and cost-effective, population preventive strategies.

## CONCLUSIONS

Asthma remains a major public health problem in Australia and many other Western countries. Asthma is a complex disorder which occurs when the respiratory tracts of genetically predisposed individuals are exposed to sufficient environmental insults. With the advent of the human genome project, genetics promises to become the foundation of new public health strategies. Research into the genetics of asthma is complicated by the underlying traits of atopy and BHR being polygenic traits with substantial gene-environment interactions. Although a number of plausible candidate genes on chromosomes 5, 11, and elsewhere have already been identified, most of the relevant genes still remain to be discovered. At the present state of knowledge, population screening for the asthma genes identified so far cannot be justified. Gene therapy for asthma is an even more remote prospect. However, the genetics of common diseases is a rapidly advancing area, upon which public health practitioners would be well advised to keep an eye.

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